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PIPER BETEL L.: A REVIEW OF PHYTOCHEMICAL AND PHARMACOLOGICAL PROFILE

Sonia Saini

Department of Botany, Isabella Thoburn College, Lucknow (U.P) India.

ABSTRACT

Piper betle Linn. (*Chavica betle*) an important species of the Piperaceae family, is a climber that grows in India, Indonesia, Malaysia, the Philippines, Sri Lanka, Vietnam, and China with glossy heart-shaped leaves that are magnificent reservoirs of phenolic compounds with antiproliferative, antimutagenic, antibacterial and antioxidant properties. Phytochemical studies show that Piper betle contains a wide variety of biologically active compounds whose concentration depends on the variety of the plant species. Many research studies on Piper betle has reported that it contains important chemical constituents such as Chavibetol, Chavibetol acetate, Caryophyllene, Allylpyrocatechol Diacetate, Campene, Chavibetol methyl ether, Eugenol, a-Pinene, f-Pinene, u-Limonene, Saprobe, 1-8-cineol and Allylpyrocatechol monoacetate. These components are valued as a stimulant for its medicinal properties like antiplatelet, antiinflammatory effects as well as immunomodulatory, gastroprotective and antidiabetic activity. This review is focused on emphasizing the varied pharmacological properties of Piper betle Linn. and its future prospects for improved usage in treating numerous conditions.

Introduction:

Medicinal plants are of proven value as potential therapeutics with the increase of resistant pathogens to commonly used antibiotics and the emergence of new infectious diseases. Extracts of the Piper betel leaf are shown to be effective against several human pathogens, although the mechanisms involved have not been elucidated. The stems are dichotomous, articulate, swollen, and rooted at nodes 3mm in diameter, woody, and with 4–2.5cm-long internodes. The leaves are simple, spiral, and exstipulate. The petiole is 5mm long, channeled, and pubescent. The blade is 10cmx6cm – 9.5cmx5cm, ovate to ovate–oblong, and light green below. The base of the blade is cordate and the apex is acuminate. The secondary nerves are in three pairs. The inflorescence is an axillary spike, which is 5.5cm long. The fruits are drupaceous, orange, and 3mm in diameter. (Christophe, 2006; Chopra, 1946)

Traditional uses

The leaf, mixed with areca nut and lime, is used as a stimulant masticatory (Rimando *et al*., 1989) and to preserve teeth (Watt *et al*., 1962). The leaves are used as a mouth freshener, for their wound healing property, and to stimulate digestive and pancreatic enzymes (Bhattacharya *et al*., 2007). The leaf is used as a carminative, aphrodisiac, tonic, laxative and to improve the appetite (Ghosh *et al*., 2005).The fresh crushed leaves are used externally to cure cuts and wounds and as a poultice for boils in the Philippines (Rimando *et al*., 1989). The fresh leaf is used as an antiflatulent in Thailand (Chaveerach *et al*., 2006).The leaves and the sap are used to cleanse wounds (Perry *et al*., 1980).The roots are used for treating rheumatism (Thanh *et al*., 1996/1997). The plant has been used to remedy "gravel" and as a diuretic (Watt *et al*., 1962). The leaf extracts are antibacterial which benefits to treat purulent parodontosis. A poultice of the leaves and a decoction has been used to remedy wounds, burns, impetigo furunculosis, eczema and lymphangitis. The decoction of this plant was found to be an effective long-lasting oral contraceptive (Thanh *et al*., 1996/1997). *Piper betel* is still in use from its fresh leaves for the healing property and chewing in the combination of areca nut and lime wrapped in betel leaf, called"betel quid" as a stimulant masticatory in Thailand, especially in the rural areas. It is one of the most important and popular medicinal plants in Thailand. It has been consumed by 200-600 million betel quid chewers around the world (Chatterjee,*et al*, 1992).

Previous Biological Investigation

The extracts of *Piper betel*, *Catharanthus roseus*, *Dendropthoe petandra* and *Curcuma mangga* Val. exhibited T47D cell proliferation and showed DPPH scavenging activity antioxidant activity (Widowati, W., *et al*, 2011). The petroleum ether extract displayed highest antioxidant activity followed respectively by ethyl acetate methanol and aqueous extracts. None of the extracts showed the best results for their antihaemolytic activity (Chakraborty, D and Shah, B., 2011). Allylpyrocatecol and chavibetol have shown protection against photosensitizationmediated lipid peroxidation of rat liver mitochondria, allylpyrocatechol was found to be more potent than chavibetol (Mula, S., *et al*, 2008). The extracts from *Piper betel* leaf extract exhibited antioxidant activity (Arambewela, L., *et al*, 2006). Allylpyrocatechol, chavibetol and the ethanol extract showed antioxidant activity; allylpyrocatechol exhibited the best results in all the in *vitro* experiments (Rathee, J., *et al*, 2006). The ethanol extract of *Piper betel* leaf showed anti-oxidant activity against erythrocytes from patients with HbE-beta thalassemia (Srimani, P., *et al*, 2009). The water, methanol ethyl acetate and petroleum ether of *Piper betel* leaves were evaluated for their antioxidant (Fathilah, A.R., 2011). The leaves showed antioxidant properties (Thanh *et al*., 1996/1997). The essential oil with fifty two volatile constituents was screened for antibacterial activity against one Gram positive, two Gram negative bacteria and yeast (Kumar, R., *et al*, 2009). The leaves extracted with ethanol had a potent antibacterial action against *Staphylococcus aureus* and *Streptococcus sp.* (Savaspun *et al*., 2003). The essential oil showed antimicrobial activity against a wide range of microorganisms. Eugenol, chavibetol acetate, 4-allylphenyl acetate and 4-allylphenol were its main components. The ethanol extract showed a healing property effect against indomethacin-induced stomach ulceration in rats (Bhattacharya, S., *et al*, 2007). Thewater, methanol ethyl acetate and petroleum ether of *Piper betel* leaves were tested against four different bacteria (*Streptococcus pyogenes, Staphylococcus aureus, Proteus vulgaris and Escherichia coli*) and antihaemolytic activities. The aqueous extracts of *Piper betel* and *Psidium guajava* exhibited antimicrobial activities with their MIC values in the range of 2.61 to 4.69 mg/mL (Fathilah, A.R., 2011). The aqueous extract exhibited maximum inhibition against *Staphylococcus aureus,* ethyl acetate extract found its inhibition against *Escherichia coli* ether extract was active against *Proteus vulgaris*. Safrole, isolated from *Piper betel* inflorescences showed bactericidal activity and released superoxide anions by polymorphonuclear leukocytes. Hydroxychavicol had an effect on phagocytic activity, the intracellular production of reactive oxygen species and the activity of the lysosomal enzyme myeloperoxidase (Chang, L.-Y., *et al*, 2009). Hydroxychavicol isolated from the aqueous extract of *Piper betel* leaf was active against oral cavity pathogens (MICs in the range of 62.5 to 500 µg/mL), it showed potent antioxidant and anti-inflammatory activity (Sharma, S., *et al*, 2009). This plant exhibited showed antimicrobial activity (Rimando *et al*., 1986). The essential oil had a bactericidal effect which can be used to treat the nose affections of the mucous membrane of and throat (Perry *et al*., 1980). The aqueous and methanol extracts of *Piper betel* leaf and other two plants were evaluated against antimicrobial activity against ten Gram positive, twelve

Gram negative bacteria. Only the methanol extract of *Piper betel* exhibited the most active against *Steptococcus species*. None of active compounds have been isolated as yet (Nair, R., *et al*, 2008). The *Piper betel* extract showed moderate activity against *Bacillus cereus*. (Vaghasiya, Y., *et al*, 2007). The leaves showed antibacterial properties (Thanh *et al*., 1996/1997) The ethanol extract of *Piper betel* leaf showed anti-inflammatory activity possibly mediated by allylpyrocatechol (Sarkar, D., *et al*, 2008). The leaf extract showed gastrocytoprotective properties. Its leaf extract has been investigated for anti-inflammatory activity (Bhattachaya *et al*., 2007). Allylpyrocatechol showed significant lowering of pro-inflammatory (Th1) cytokine levels in arthritic paw tissue at doses levels of 2 and 4 mg/Kg p.o. and enhanced the production of anti-inflammatory (Th2) cytokines IL-4 and IL-5 by cytometric bead array immunoassay (Pandey, A., *et al*, 2010). Hydroxycharvical showed ulcer healing activity compared to omeprazole (Yadove, S., *et al*, 2008). The *Piper betel* extract showed proinflammatory potency. (Vaghasiya, Y.,*et al*, 2007). The various extracts of eight medicinal plants inclding *Piper betel* showed antifungal activity against plant pathogen (Prince, L. and Prabakaran, P., 2011). The aqueous leaf extract of *Piper betel* exhibited antifungal activity against 124 strains of selected fungi with MIC in the range of 15.62 to 500 µg/mL for yeasts, 125 to 500 µg/mL for *Aspergillus species* and 7.81 to 62.5 µg/mL for dermatophytes (Ali, I., *et al*, 2010). The aqueous extract from the leaves had antifungal activity against *Phaeoisariopsis personata* and *Puccinia Arachidis* in *vitro* (Krishna *et al*., 2005).

The leaf extract showed gastrocytoprotective properties. Its leaf extract has been investigated for antifungal activity (Bhattachaya *et al*., 2007). The methanolic and aqueous ectracts of *Piper betel* exhibited strong activity against *Candida albicans* and *Malassezia pachydermatis* (found in skin of animals). The leaves extracted with ethanol had a potent antifungal activity against *Trichophyton mentagrophyte* (Savaspun *et al*., 2003). The essential oil and the leaf extracts also had antifungal activity against *Aspergillus niger*, *Aspergillus oryzae*, *Curvularia lunata*, and *Fusarium oxysporum* (Duke, 1929). The chloroform extract from fresh frozen leaves has investigated for antifungal activity against *Cladosporium cucumerinum* (Evans *et al*., 1984). The ethanol extract of this plant inhibited fungal pathogen of plant (Mohamed *et al*., 1996). This plant showed fungicidal activity (Rimando *et al*., 1986). The dried powder of the leaves showed antifungal activity against the fungal pathogen causing Chalkbrood disease in honey bee larvae (Chantawanakul *et al*., abstract). The leaves showed antifungal activity against a fungal pathogen of rice (Tewari *et al*., 1984). The extract also acted as a protective agent in the early phase of wound healing by increasing total protein content and wound contraction rate in rats (Keat, E., C., *et al*, 2010). The aqueous and methanol extracts of *Piper betel* leaf and other two plants were evaluated against *Candida tropicalis*. Only the methanol extract of *Piper betel* exhibited the most active against *Candida tropicalis*, (Nair, R., *et al*, 2008). The ethanol and essential oil extract of *Piper betel* leaf possess antihistaminic activity on isolated guinea pig tracheal chain preparation (Hajare, R., *et al*, 2011). The extract of *Piper betel* leaves showed potent xanthine oxidase inhibition, hydroxychavicol was isolated as an active principle (Murata, K., *et al*, 2009). The ethanol extract from *Piper betel* accelerated intestinal transit in mice up to 90% at 800mg/Kg (Dhaked, P., S., *et al*, 2010). The hexane and chloroform fractions exhibited activity against human lymphatic filarid *Brugia malayi* and triggered an immune response in mice (Singh, M., *et al*, 2009). The methanolic extract from two landrances of *Piper betel* showed its pro-apoptotic effect on *Leishmania donovani*, possibly attributable to its high content in eugenol (Mira, P., *et al*, 2009). The expectorant effect found from the leaves was used for coughs, asthma and bronchitis (Chaveerach *et al*., 2006).

In addition, this plant showed hypotensive, cardiac and respiratory depressant effects, smooth and skeletal muscles relaxant action and nematocidal activity (Rimando *et al*., 1986). ydroxychavicol isolated from *Piper betel* leaf inhibited platelet aggregation and it could be the agent to prevent and treatment of atherosclerosis, other cardiovascular through its anti-inflammatory and antiplatelet effects on hemostatic functions (Chang, M., C., *et al*, 2007). Its essential oil showed hypotensive, cardiac and respiratory effects (Thanh *et al*., 1996/1997). The alcoholic extract of the leaf-stalk has significant antifertility effects in both male and female rats (Ghosh *et al*., 2005). The methanol extract containing phenols, flavonoids, tannins and polysaccharides was active to various immune disorders including autoimmune disorders (Kanjwani, D., G., *et al*, 2008). The extracts of the leaf was investigated for inhibitory activities against HIV-1 intergrase with 76.32±0.68 % (chloroform extract), 49.86±4.02 % (methanol extract) and 36.43±4.07 % (water extract) of inhibitions (Tewtrakul *et al*., 2006). The ethanol extract of *Piper betel* leaf exhibited cytotoxicity activity in the brine shrimp (*Astemia salina* Linnaeus) assay. Chavibetol and allylpyrocatechol were the active compounds with LC50 values 2.55 and 16.36 µg/mL at 24 h., respectively (Koocharoenpisal *et al*., 1997). Hydroxychavicol showed biotransformation and cytotoxic effects in isolated rat hepatocytes (Nakagawa, Y., *et al*, 2009). The methanol extract of *Piper betel* leaf investigated for antimalarial activity against *Plasmodium berhei* infections. The extract demonstrated significant schizonticidal activity in three antimalarial evaluation models and showed toxicologically safe (Al-Adhroey, A.H., *et al*, 2011).

CONCLUSION:

This review suggests that the leaves of Piper betle have a tremendous potential as a potent source for novel therapeuticusage. The pharmacological profile reveals it to be fit for its future usage as a promising source for treating various conditions Therefore, in the near future the standardization and stabilization studies on the leaf extract can be carried out which can help in improving its usage for varied medicinal usage.

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